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Decreased HIV-specific T-regulatory responses are associated with effective DC vaccine-induced immunity

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BACKGROUND

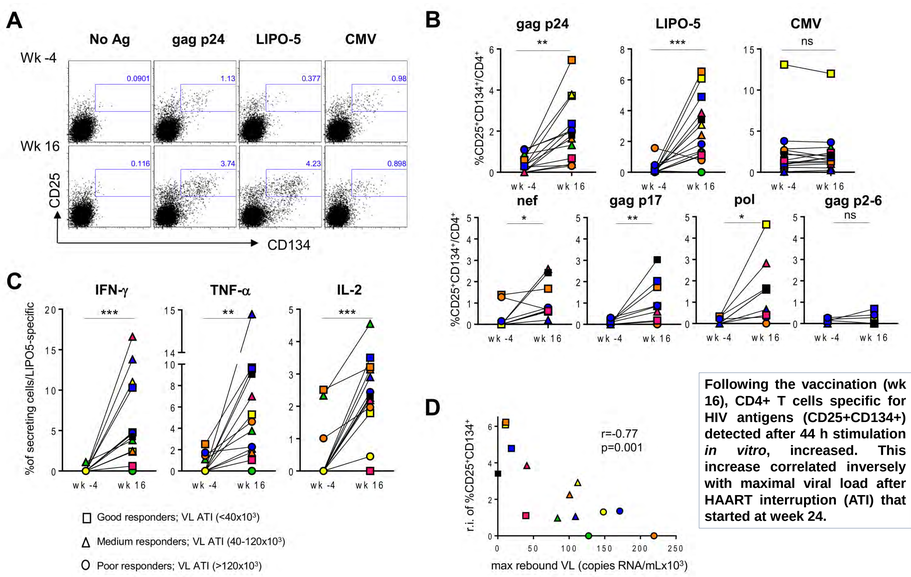
The role of regulatory T cells (Tregs) in vaccination has been poorly investigated. We have reported that vaccination with ex vivo-generated dendritic-cells (DC) loaded with HIV-lipopeptides (LIPO-5-DC vaccine) in HIV-infected patients was well tolerated and highly immunogenic. These responses and their relation to viral replication following analytical treatment interruption (ATI) were variable. Here, we investigated whether the presence of HIV-specific Tregs might explain these differences.

METHODS

Fourteen HIV-1 infected individuals under successful antiretroviral therapy have been included in this study. Patients received LIPO-5-DC vaccine every 4 weeks during 16 week period. Blood was drawn 4 weeks prior to first vaccination (week -4) and 4 weeks after the last (week 16). HAART was interrupted 8 weeks after the last injection (week 24). Co-expression of CD25, CD134, CD39 and FoxP3 was used to delineate both antigen-specific Tregs and effectors T cells (Teffs).

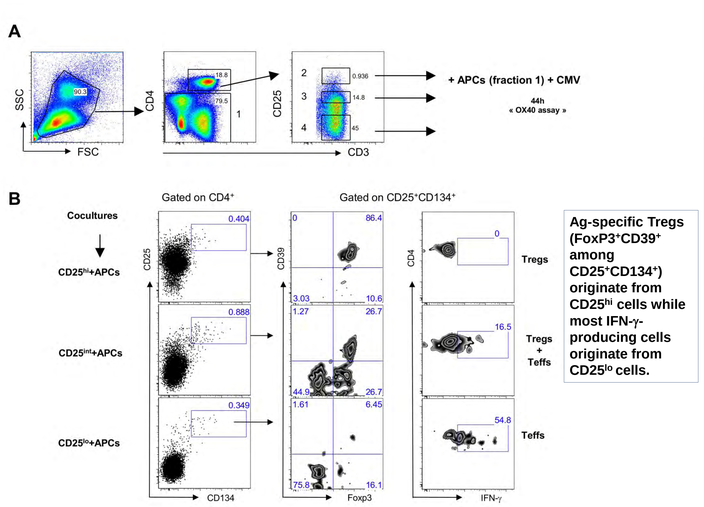
RESULTS

HIV-specific responses are upregulated after the vaccination with LIPO-5-DC vaccine



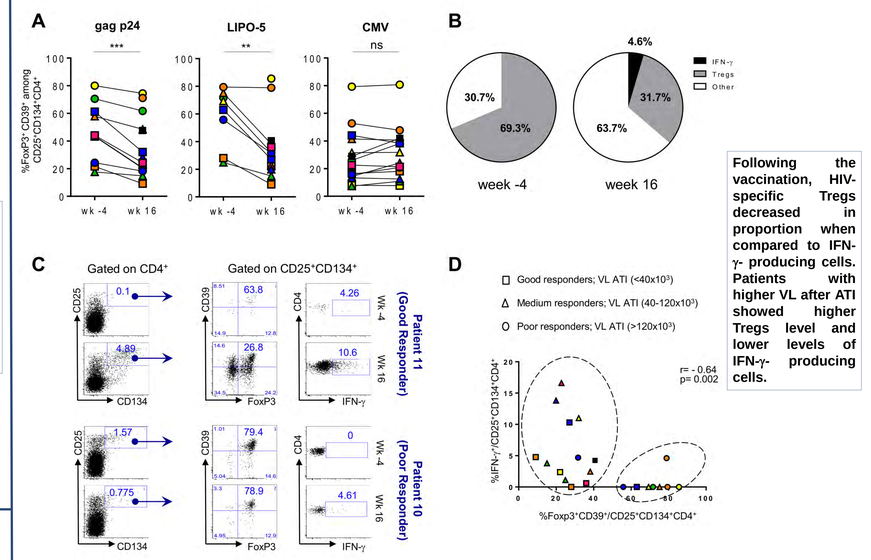
Following the vaccination (wk 16), CD4+ T cells specific for HIV antigens (CD25+CD134+) detected after 44 h stimulation *in vitro*, increased. This increase correlated inversely with maximal viral load after HAART interruption (ATI) that started at week 24.

Antigen-specific Tregs originate from CD25^{hi} cells



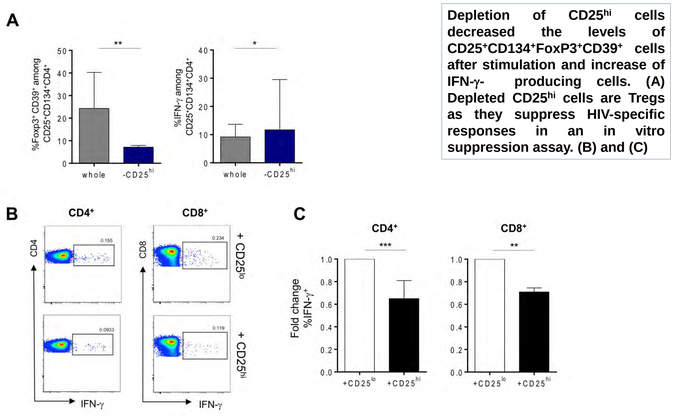
Ag-specific Tregs (FoxP3$^+$CD39$^+$ among CD25$^+$CD134$^+$) originate from CD25^{hi} cells while most IFN-γ-producing cells originate from CD25^{lo} cells.

HIV-specific Tregs/Teffs ratio is affected by vaccination



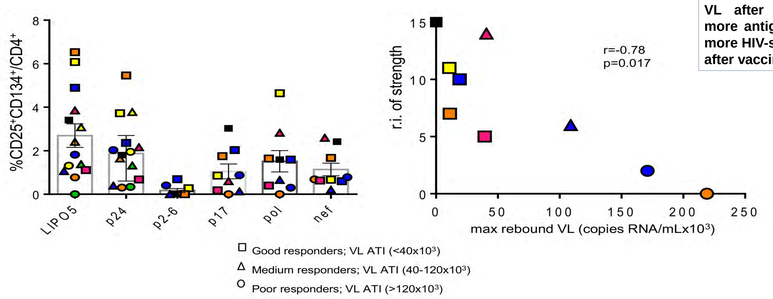
Following the vaccination, HIV-specific Tregs decreased in proportion when compared to IFN-γ- producing cells. Patients with higher VL after ATI showed higher Tregs level and lower levels of IFN-γ- producing cells.

Tregs can suppress HIV-specific responses in vitro



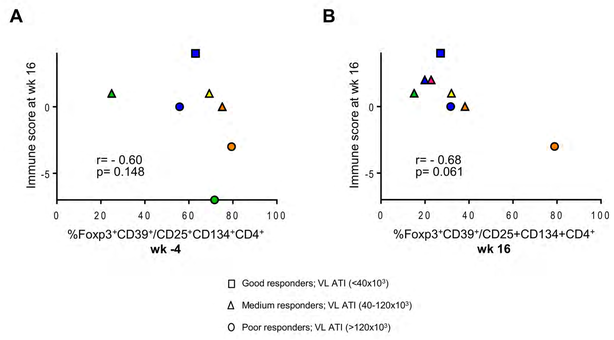
Depletion of CD25^{hi} cells decreased the levels of CD25$^+$CD134$^+$FoxP3$^+$CD39$^+$ cells after stimulation and increase of IFN-γ- producing cells. (A) Depleted CD25^{hi} cells are Tregs as they suppress HIV-specific responses in an in vitro suppression assay. (B) and (C)

Overall strength of the HIV-specific responses is inversely correlated with viral load after ATI



Patients with lower levels of VL after ATI responded to more antigens and harboured more HIV-specific CD4+ T cells after vaccination (strength).

Patients with lower HIV-specific Tregs respond better to vaccination



Multivariate immune scores correlated inversely with levels of HIV-specific Tregs. This demonstrates the impact of HIV-specific Tregs on immune responses induced by LIPO-5-DC vaccine.

CONCLUSION

We report that HIV-infected individuals harbor high levels of HIV-specific Tregs at baseline. The LIPO-5-DC vaccine preferentially induces Teffs responses and shifts the HIV-specific Tregs:Teffs ratio towards polyfunctional effector responses that inversely correlate with viral load rebound after treatment interruption. Interestingly, vaccinees who display lower levels of HIV-specific CD4$^+$CD134$^+$CD25$^+$CD39$^+$FoxP3$^+$ Tregs show better responses to the LIPO-5-DC vaccine.

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